SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Viramune. This scientific discussion has been updated until 1 March 2004. For information on changes after this date please refer to module 8B

1. Introduction

Current options for the treatment of Human Immunodeficiency Virus (HIV) infected patients consist of nucleoside analogue reverse transcriptase (RT) inhibitors and protease inhibitors. The first category of agents acts at an early stage in the HIV life cycle by blocking the activity of reverse transcriptase. This enzyme is essential for the conversion of viral RNA to proviral DNA, thus allowing integration into host cell DNA and subsequent viral replication. On the contrary, the second group of agents acts at a later stage in the viral replication. HIV protease is an enzyme essential for the production of mature, progeny virions.

A new class of antiviral agents acting on the reverse transcriptase enzyme through a different mechanism compared to nucleoside analogues RT inhibitors and classified as non-nucleoside RT inhibitors (NNRTIs) has been developed. NNRTIs bind directly to the HIV RT enzyme and blocks the RNA dependent and DNA-dependent DNA polymerase activities by causing a disruption of the enzyme catalytic site.

Nevirapine, which is the first representative of this new class to be submitted for registration, is the active substance of Viramune. This medicinal product containing 200 mg of nevirapine has been developed as an oral therapy (tablet) for the treatment of HIV-1 infection.

During the evaluation of the tablets, the need for the development of a liquid formulation was identified for the treatment of children and adults who have to swallow tablets and an oral suspension containing 50-mg/5 ml of nevirapine has been developed and later submitted.

2. Chemical, pharmaceutical and biological aspects

As the quality variations submitted since the marketing authorisation was granted had no major impact on the safety/efficacy of Viramune, the quality scientific discussion below reflects the data submitted in support of the initial marketing authorisation. See "Steps taken after granting the Marketing Authorisation" for information on quality variations.

Composition

Viramune is presented as a conventional uncoated tablet containing 200 mg nevirapine anhydrous, suitable for marketing. Viramune is supplied in opaque polyvinyl chloride (PVC)/aluminium foil laminate push-through blister units containing 10 tablets per blister card, and 6 blister cards per carton (60 tablets per carton).

Clinical trials formulations manufactured at various strengths (2.5 to 200 mg) were essentially identical to that of the commercial market. The only difference consisted of the grades of polyvidone used as a binder. However all formulations showed acceptable and comparable dissolution profiles.

A preserved aqueous-based oral suspension containing nevirapine hemihydrate with the quantity adjusted to provide the equivalent of 50-mg/5 ml anhydrous nevirapine has been later developed. Viramune oral suspension is supplied in a white high-density polyethylene (HDPE) bottle capped with a two piece child-resistant closure with a low density polyethylene (LDPE) foam liner. Each bottle contains 240 ml of oral suspension. A clear polypropylene 5 ml (0.2 ml graduations) dispensing syringe is provided to facilitate accurate administration of the dose. Acceptable data demonstrating the precision and accuracy of the dosing syringe were provided. During the clinical development of the suspension and paediatric indication, several strengths of tablets and oral suspension (25 and 50 mg/5ml) were used. The clinical trial formulation of the oral suspension was shown to be bioequivalent to the formulation intended for marketing. The HDPE bottle material is inert and was shown to be compatible with the active substance and other ingredients of the formulation.

Pharmaceutical development

Nevirapine is selected from the series of dipyridodiazepones and is supplied as the free base form. The active substance can exist in two pseudopolymorphic forms, anhydrous and hemihydrate. The anhydrous form was selected for the development of the oral tablet due to its higher intrinsic aqueous solubility (90 µg/ml at 25°C). Nevirapine is a weak base showing increased solubility at acidic pH values. The development of an immediate release uncoated tablet was adequate to promote a maximal dissolution rate of the active substance. The anhydrous form was shown to be non-hygroscopic, and conversion to the hemihydrate form did not occur even in samples exposed to 92 % relative humidity for 24 months at 30°C. Similarly, it was demonstrated that although a wet granulation was used, conversion did not occur during wet granulation or any step of the manufacturing process.The standard wet granulation process was selected since it provided good flow characteristics and ease of manufacture. The tablet dissolution was found to be correlated with the particle size of the active substance. Milling of nevirapine was therefore introduced to control active substance particle size and to maximise dosage form dissolution behaviour. The excipients chosen for the formulation are commonly used in the manufacture of solid dosage forms.
The anhydrous form was selected for the development of the oral suspension. Adequate evidence was provided showing that no polymorphic changes occurred under normal storage or physical stressed storage conditions. The suspension is preserved with a combination of methyl and propylparabens and the levels of these preservatives have been correlated with antimicrobial effectiveness tested according to European Pharmacopeial requirements.

Method of preparation

The manufacturing process of the tablets consists of a wet granulation in which the milled active substance is dry mixed with lactose and polyvidone. The formed dried granules are milled, mixed with other excipients and compressed into tablets.

The manufacturing process is under control and ensures both batch-to-batch reproducibility and compliance with standard specifications.

Validation data presented on three batches manufactured at the US production site were sufficient to demonstrate the consistency of the process and the quality of the product. Manufacture of the tablets at the German production site was considered acceptable, provided that the company, as post-approval commitment, provides appropriate validation data on three batches. Since the planned production scale at the German site is larger, some adjustments were made to accommodate for the differences in batch sizes and capacity of the equipment.

The method of preparation of the oral suspension is standard for this form and has been adequately described. Validation data presented on three production batches manufactured using three different lots of nevirapine anhydrous were adequate to demonstrate that the process is under control and ensures both batch-to-batch reproducibility and compliance with standard specifications. Tests at release are standard and ensure reproducible clinical performance of the product.

Control of starting materials

Nevirapine anhydrous is a white to off-white crystalline powder. The quality of the active substance is guaranteed by the established specifications and the proposed analytical methods for assay and purity are adequately validated. The proposed limits are well justified.

Synthesis of nevirapine consists of a multi-step process starting from a commercially available starting material. The analytical methods used to control starting materials as well as intermediates of synthesis are acceptable. Milling has been added as an additional step to optimise dissolution.

The related impurities arising from the synthesis were characterised and the company committed to reviewing the data concerning the proposed limits for each individual impurity and total impurities, based on batch analysis results.

Nevirapine hemihydrate is a white to off-white crystalline powder which has been adequately characterised. Its synthesis has been developed in parallel to the one for the anhydrous form. The synthesis of these two crystal forms is similar until the final drying step. The analytical methods used to control starting materials as well as intermediates of synthesis are acceptable. The active substance, before being used for the manufacture of the finished product is milled in order to obtain an acceptable

particle size distribution. The synthetic pathway is adequately presented and the impurity profile is well characterised and in line with current ICH guideline. The specifications for impurities are identical to those of nevirapine anhydrous. The identified impurities arising from synthesis have been toxicologically qualified. Batch analysis data confirm that nevirapine hemihydrate complies with the specifications.

All other ingredients entering in the preparation of the tablets or the oral suspension are commonly used excipients for these formulations and meet pharmacopoeial requirements.

Control tests on the finished product

Tablets are tested according to standard methods. The chromatographic impurity profile appears to be simple since no degradation products have been detected upon storage. A standard international (ICH) recommendation is therefore used for the specifications. Considering that none of the impurities arising from the synthesis are degradation products, it is considered acceptable in the light of ICH recommendation not to have them as part of the specifications of the finished product, since they are controlled in the starting material. Certificate of analysis from eight production batches showed that results are within specifications.

Stability

Drug substance

Several pilot and production size batches of nevirapine were subject to stability studies. Results showed that nevirapine is highly stable even under stressed conditions over the period of study (24 months). No degradants were detected and all the results remained within the specifications. Additional long-term stability data will however be presented when available.
Stability data on five production batches was confirmed that nevirapine hemihydrate was stable and no degradants were detected in any of the batches both under normal and stress conditions. Based on the results provided, a re-test period for the active substance of 2 years has been defined. In addition, long-term stability data will be submitted on an ongoing basis.

Finished product

Stability studies have been carried out at room temperature and under accelerated conditions for product stored in HDPE bottle and blister packaging. Based on the results available from nine primary batches made at production scale at the US production site, only a shelf-life of 24 months is supported. No particular storage conditions to ensure the quality of the product over the shelf-life are requested. Currently no stability data from the tablets manufactured at the German production site and stored in the proposed blister pack are available. However the German site has been accepted as the only production site for Europe, based on stability data obtained from tablets produced at the US manufacturing site, upon commitment from the company to present every three months results from ongoing stability studies and to immediately report any unexpected event occurring in the manufacture.

Three primary batches were stored under normal and accelerated storage conditions. The batches were initially capped with HDPE/polypropylene closure and pulpboard liner. Deterioration of the pulpboard liner was observed at three months and another study was initiated which included a portion of the batches recapped with the liner intended for marketing. Stability data up to 18 months for the newly recapped oral suspension and 24 months with the old pulpboard liner confirmed the physical and chemical stability of the oral suspension and the antimicrobial efficacy of the preservative. These results support a shelf life of 24 months. Long-term stability data will be submitted on ongoing basis.

An in-use stability study designed to mimic the delivery of 2 ml dose, which represents one of the lowest projected doses, twice a day, using the delivery device intended for marketing has been performed. An additional study is presented on the stability of the product exposed to freeze-thaw conditions. On the basis of results from both studies, the claimed in-use shelf life of 60 days with no special storage precautions is supported.

Bioequivalence

Two main bioequivalence studies were performed with the tablet formulation. The first study involved three tablet formulations, one clinical scale and one production scale, both prepared from nevirapine

milled during the tablet manufacture, and a clinical tablet prepared from unmilled nevirapine, relative to an oral solution. A 4-way crossover comparison study showed bioequivalence between the formulations tested.

The second 3-way crossover study compared the bioavailability from three production/commercial scale batches with varying dissolution profiles. All three batches were bioequivalent with respect to systemic exposure (AUC). The significantly different values for C_{max} and t_{max} were considered not to be clinically relevant.

Further study bridging the formulations tested in the first bioequivalence trials and the final commercial one was not considered necessary since no major changes have been made to the formulation and/or manufacturing process and the dissolution profiles were found to be comparable.

Three single dose crossover studies were performed in healthy adults with the oral suspension.
The objectives of these studies were:

- to assess the relative bioavailability of nevirapine tablets and suspension compared to an oral reference solution (trial 1100.896)
- to determine the bioavailability of nevirapine suspension (using an oral syringe) relative to nevirapine marketed tablets (trial 1100.1231)
- to assess the bioequivalence of nevirapine suspension (using a dosing cup) by comparing the intended to market batch of oral suspension to a clinical batch of suspension (trial 1100.1213). In this study the suspensions were administered using a dosing cup without rising.

In studies 1100.1231 and 1100.896 in which the suspension was administered directly using a syringe, it was demonstrated that the suspension and tablet formulations were comparably bioavailable with respect to extent of absorption. In study 1100.1213 the suspension was administered in a dosing cup without rinsing. The suspension intended for marketing was bioequivalent to the suspension used during clinical trials but was not bioequivalent to the marketed tablets. This could be attributed to incomplete dosing of the two suspensions since there was about 13 % of the dose remaining in the cup.

The assessment of nevirapine bioavailability was shown not to be influenced by autoinduction provided that a crossover design is utilised with an adequate washout period between doses.

3. Toxico-pharmacological aspects

Pharmacodynamics

Nevirapine is a non-nucleoside reverse transcriptase inhibitor (NNRTI), which interrupts the reverse transcription of viral RNA to DNA, a crucial step for HIV replication, by a mechanism of action different from nucleoside analogues. Nevirapine binds directly to the HIV-1 RT enzyme and blocks the RNA-dependent and DNA-dependent DNA polymerase activities by causing a disruption of the enzyme catalytic site. The covalent binding sites of nevirapine are tyrosine residues 181 and 188. Due to the absence of tyrosine residues in these positions of HIV-2, nevirapine is inactive against HIV-2 RT. The activity of nevirapine does not compete with template or nucleoside triphosphates. Eukaryotic DNA polymerase (such as human DNA polymerases α, β, γ, δ) are not inhibited by nevirapine.

Studies on pharmacodynamic effects with respect to the proposed indication showed that nevirapine is a potent and specific inhibitor of HIV-1 RT. A concentration of 40 nM completely inhibited the enzyme. Nevirapine was found to be a potent inhibitor of HIV-1 replication in human T-cells line, which suggested that it specifically inhibited an early stage of HIV-1 replication. The antiviral activity investigated *in vitro* revealed that nevirapine is active against a broad range of HIV-1 strains, including clinical strains and zidovudine-resistant mutants. The dose required to inhibit the viral replication by 50 % (IC_{50}) ranged from 10nM-100nM.

In vitro studies of nevirapine in combination with other nucleoside analogues revealed that nevirapine and zidovudine (ZDV) at various concentration ratios showed marked synergism in inhibition of HIV-1 replication. Furthermore, the combination nevirapine/ZDV plus one other antiretroviral such as didanosine (ddI), lamivudine or stavudine was investigated. In all combination regimens, nevirapine had either a synergistic or additive effect.

The pharmacology safety programme addressed among others, effects on central and autonomous nervous system, cardiovascular, renal, respiratory systems and did not reveal any severe side effects at relevant dose levels and/or concentrations.

The cellular toxicity of nevirapine was tested. The results indicated that nevirapine is active in a dose range significantly below the levels of cell toxicity. No cellular toxicity was observed with any of the tested drug combinations as mentioned above.

Pharmacokinetics

The pharmacokinetic profile of nevirapine was determined in mouse, rat, dog, cynomolgus monkeys and chimpanzees using well characterised radiolabelled nevirapine and validated HPLC-UV methods.

Absorption and distribution

Orally administered nevirapine was well absorbed. In the different animal species studied the absolute bioavailability ranged from 30 % (in dog) to 70 % (in cynomolgus monkeys). The t_{max} varied considerably in cynomolgus monkey (t_{max} 1-4 hours) and in chimpanzees (t_{max} 6-30 hours) showing that the absorption was very slow. In humans, nevirapine was shown to be readily absorbed after oral administration with a t_{max} around 4 hours.

In all animal species studied, plasma protein binding, at non saturating concentrations was moderate ranging from 44 % to 62 %.

Tissue distribution studies in rats and cynomolgus monkeys showed that nevirapine widely distributed in the body penetrated the central nervous system and lymphoid system. In the rat, 8 hours after a single oral dose of radiolabelled nevirapine, the levels of radioactivity in the brain were about 15-30 % of those found in the plasma.

Tissue distribution after repeated dosing was only investigated in pregnant animals. Results showed that nevirapine crosses the placental barrier and were found in the breast milk.

Biotransformation

In all animal species studied including humans, nevirapine was extensively metabolised. Nevirapine was found to undergo major oxidative metabolism followed by glucuronidation. No major difference in the metabolic profile was noted between species. In rats and dogs, nevirapine was shown to induce its own hepatic metabolism.

Potential pharmacokinetic interactions between nevirapine and antiretroviral nucleoside analogues/protease inhibitors were not studied in animals. However, interaction studies have been carried out in humans.

Excretion

Nevirapine was rapidly eliminated and appeared to be highly species dependent with a rapid elimination in rat, mouse, dog and cynomolgus monkey ($t_{1/2}$ 0.4-1.5 hours) whereas elimination was slower in chimpanzees ($t_{1/2}$ 16 hours). Elimination was also found to be slow in humans ($t_{1/2}$ 45 hours after single dose of nevirapine). In all species, except the dog, the major route of elimination was renal (65 to 78 % of radioactivity was recovered in urine). In the dog, this pattern was reversed with 70 % of the radiolabelled eliminated in faeces. Nevirapine and its metabolites were shown to undergo enterohepatic cycle in rats.

The pharmacokinetic profile of nevirapine after repeated administration was established based on toxicokinetic data obtained from the major toxicology studies. In rats, nevirapine exposure was roughly proportional to the administered dose over a range of 5-150 mg/kg whereas in dog no linearity was found. In both species, autoinduction occurred during prolonged administration resulting in a decrease of systemic exposure to nevirapine.

Toxicology

Interspecies dose extrapolation was based on toxicokinetics data taking into account the decrease in systemic exposure observed in both rats and dogs following prolonged treatment. Based on the estimated human exposure to nevirapine at the maximum therapeutic dose level (i.e. 400 mg/day), there seemed to be acceptable safety margins.

Single dose toxicity was studied in rodent, dogs and cynomolgus monkeys with doses ranging from 20 to 3200 mg/kg. These studies revealed that the acute toxicity of nevirapine was low after orally administration. At high doses, nevirapine had depressed the central nervous system functions of all the species studied, resulting in sedation and decreased motor activity.

Repeated dose toxicity was studied in mice (13 weeks), rats and dogs up to 52 weeks. In all three species, the main target organs of toxicity were liver and lymphoid tissues. Centrilobular hepatocellular hypertrophy found in the liver of all species and hypertrophy of thyroid follicular cells seen in rats were probably due to enzyme induction. Lymphoid organs were depleted in all species tested. A direct effect of nevirapine on the immune system cannot therefore be excluded. Upon prolonged nevirapine administration, all three species developed skin lesions such as dermal swelling and/or erythema. Rats also developed scabbing and ulcerative skin lesions. Referring to the dog, an immunosuppressive action of nevirapine was suggested; especially since the skin changes noted were primarily of a secondary infectious nature. Although this immunosuppresion was suggested to be species-specific since the immunotoxicity screen in rodents was negative, further investigation was considered necessary to address this point. The lung changes observed in several dogs tested at high doses were considered to be of a secondary infectious and not primary toxicological nature, possibly associated with immunological alterations suspected in this species.

A complete programme of reproductive toxicity studies was conducted. These studies did not reveal any significant effects on fertility. Following administration of nevirapine to rats and rabbits during the organogenic period, embryotoxicity only occurred at doses causing maternal toxicity.

In a standard battery of *in vivo* and *in vitro* tests, no genotoxic potential of nevirapine was found.

Carcinogenicity studies performed in rodents were not available at the time of the recommendation for the granting of a marketing authorisation, which was considered acceptable. Results from the carcinogenicity studies submitted as part of the follow-up measures to be fulfilled post-authorisation, showed that nevirapine induces hepatic tumours in rats and mice. In rats these findings are most likely related to nevirapine being a strong inducer of liver enzymes, and not due to a genotoxic mode of action. The mechanism of tumours in mice is not yet clarified and therefore their relevance in humans remains to be determined.
Local tolerance studies did not reveal any irritating or sensitising potential of nevirapine. The haemolysis observed in intravascular testing was attributed to the vehicle used.

Environmental risk assessment did not foresee any toxicological risk for the environment with nevirapine.

With respect to the intermediates in the synthesis of nevirapine, no potential toxicity was found.

All toxicity studies were conducted in compliance with current Good Laboratory Practices.

Considering that nevirapine hemihydrate which is the pseudopolymorphic form used in the oral suspension formulation is produced by the same synthetic schemes as the anhydrous tablet form but has not been dried, the two forms could therefore be considered equivalent with respect to impurity levels. Additional preclinical toxicology testing was therefore not considered necessary.

4. Clinical aspects

Pharmacokinetics

Adults

The pharmacokinetic profile of nevirapine was investigated in 9 trials involving healthy adult volunteers and HIV-infected patients of both sexes.

Absorption and distribution

Nevirapine was readily absorbed (> 90 %) after oral administration in healthy volunteers and in adults with HIV-1 infection. Following an oral single dose of 50 mg tablet formulation, the bioavailability in 12 healthy adults was 93 ± 9 % (mean standard deviation). Peak plasma nevirapine concentrations (C_{max}) of 2 ± 0.4 μg/ml were attained by 4 hours (t_{max}) following a single 200 mg dose. Following multiple doses, nevirapine steady-state peak concentrations appeared to increase linearly in the dose range of 200 to 400 mg/day. Steady-state trough nevirapine concentrations evaluated in 242 volunteers were 4.5 ± 1.9 μg/ml, at 400 mg/day dosing.

The influence of food on the pharmacokinetic parameters was investigated. When 200 mg nevirapine was administered to 24 healthy adults (12 female, 12 male), with either a high fat breakfast or antacid, the extent of nevirapine absorption (AUC) was comparable to that observed under fasting conditions, however in both cases, C_{max} was reduced, t_{max} was delayed and the time to 50 % absorption was at least doubled when compared to fasted conditions. In a separate study involving 6 HIV-1-infected patients, nevirapine steady-state systemic exposure (AUC) was not significantly altered by ddI, which is formulated with an alkaline buffering agent.

The *in vitro* plasma proteins binding of nevirapine were 60 % over a concentration range of 1-10 g/ml. Nevirapine is lipophilic and is essentially nonionised at physiologic pH. Following intravenous administration to healthy adults, the volume of distribution (Vdss) was 1.21± 0.09 l/kg, suggesting a wide tissue distribution. Nevirapine readily crosses the placenta and is found in breast milk. Nevirapine concentrations in human cerebrospinal fluid (n = 6) were 45 % ± 5 % of the concentrations in plasma; this ratio is approximately equal to the free fraction. Considering the low penetration of other antiretrovirals in central nervous system (CNS), this property could represent an advantage but further data related to viral load reduction or resistance emergence in CNS were not available at the time of the recommendation for the granting of a Marketing Authorisation. Results from two sub-studies (1100.1204 and 1100.1224) in adults submitted as part of the follow-up measures to be fulfilled post-authorisation, showed that the ratio of median nevirapine concentrations in cerebrospinal fluid (CSF) and plasma was 0.49 and the CSF HIV viral load was suppressed below 50 copies/ml in all evaluable patients. A further sub-study, which was a post-hoc descriptive analysis from the ACTG 245 study in paediatric patients, showed that the evolution of resistance mutations was similar in paired plasma and CSF fluid samples. It hence appears that CNS does not act as a protected site against emergence of virus resistance, although nevirapine penetrates the CSF to a greater extent than concomitant antiretroviral therapy.

Biotransformation

In humans, nevirapine is extensively metabolised via the oxidative cytochrome P450 to several hydroxylated metabolites, which subsequently are glucuronised. *In vitro* studies with human liver microsomes suggested that the metabolic pathway was primarily mediated by cytochrome P450 isozymes from the CYP3A family and to a lesser degree CYP2B6.

Excretion

In a mass balance/excretion study carried out in eight healthy male volunteers, at steady-state approximately 91% of a 50 mg radioactive dose of nevirapine was recovered, of which 81 % was excreted in urine and 10 % in faeces. Greater than 80% of the radioactivity in urine was made up of glucuronide conjugates of hydroxylated metabolites. Three major metabolites were found in urine:
2-hydroxy-nevirapine glucoronide, 3-hydroxy-nevirapine glucoronide and 12-hydroxy-nevirapine glucoronide. Thus cytochrome P450 metabolism, glucuronide conjugation, and urinary excretion of

glucuronidated metabolites represent the primary route of nevirapine biotransformation and elimination in humans. Less than 3 % of nevirapine was excreted unchanged.

Nevirapine has been shown to be an inducer of hepatic cytochrome P450 metabolic enzymes. This autoinduction resulted in 1.5 to 2 fold increase of the apparent oral clearance of nevirapine as treatment continued from a single dose to two-to-four weeks of dosing with 200-400 mg/day. Subsequently, the terminal phase half-life of nevirapine in plasma decreased from 45 hours (single dose) to 25-30 hours following multiple dosing with 200-400 mg/day.

Although the apparent volume of distribution (Vdss/F) of nevirapine was found to be slightly higher in females subjects (1.54 l/kg) compared to males (1.38 l/kg), no significant gender difference in nevirapine clearance or plasma concentrations following single or multiple oral doses administrations were observed.

No study was specifically designed to evaluate the difference in metabolism between race. Nonetheless, based on pooled data from several clinical trials, an evaluation of nevirapine plasma concentrations from HIV-1-infected patients (Black, Hispanic and Caucasian) showed no marked difference in nevirapine steady-state trough concentrations.

Children

The pharmacokinetic profile of nevirapine was not established in children at the time of the granting of the Marketing Authorisation. It has been later determined in a single dose study in 9 patients aged between 9 months and 14 years administered after an overnight fast (3 patients per dose level equivalent to 7.5 mg/m², 30.0 mg/m² and 120.0 mg/m²). Nevirapine was readily absorbed following single oral administration of 7.5 mg/m², 30.0 mg/m² and 120.0 mg/m² with peak plasma concentrations of 0.3 ± 0.07 µg/ml, 0.7 ± 0.2 µg/ml and 2.9 ± 0.2 µg/ml respectively. Peak plasma nevirapine concentrations of 2 ± 0.4 µg/ml were attained by 4 hours following a single 200 mg dose. AUC and Cmax increase proportionally with the dose. The same pattern has been observed in adults. Following absorption nevirapine mean plasma concentrations declined log linearly with time. Nevirapine oral clearance was 0.91 ± 0.15 l/ m²/h and the terminal half-life was 30.6 ± 10.2 hours whereas in adults it corresponded to approximately 45 hours. Nevirapine clearance and half time correlated with age in paediatric patients.

A population pharmacokinetic analysis using data from a phase I/II clinical study including 37 children (study 1100.882) who received nevirapine alone or in combination with ZDV and/or ddI, suggest that body surface area (BSA) and body weight (BW) explained the interpatient variation in nevirapine clearance. Nevirapine clearance increased non-linearly with BW. In contrast to the BSA model, average nevirapine clearance adjusted by BW was closer in value among infants (110 ± 23 ml/kg/hour), younger children aged 1 to 4 years (120 ± 22 ml/kg/hour) and children aged 4 to 8 years (102 ± 17 ml/kg/hour) compared to that observed in children older than 8 years (50 ± 10 ml/kg/hour). In this group values were comparable to those reported in adults receiving 400 mg/day. The clearance values were lower in the youngest children (less than one year) and the range of values observed in this age group was wide. As observed in adults, nevirapine apparent clearance in children was higher following multiple dose treatment compared to a single dose administration suggesting that nevirapine is autoinducer of metabolism in children also. Further details are set out in section 5.2 of the SPC.

The pharmacokinetic behaviour of nevirapine has not been assessed in elderly.
The pharmacokinetic behaviour of nevirapine was not established in patients with renal impaired function and hepatic impaired function at the time of granting of the Marketing authorisation. Post-authorisation, study 1100.1259, an open label, single dose (200 mg) study involving 23 non-HIV infected patients with stable renal dysfunction and 10 non-HIV infected patients with hepatic dysfunction was conducted to study the pharmacokinetics of nevirapine in these patients. There were 8 healthy controls.
In patients with renal insufficiency not requiring dialysis non-significant changes of nevirapine pharmacokinetic parameters were found. In dialysed patients, a 43,5% reduction in nevirapine AUC over one week as well as a reduction of nevirapine half-life was found. Nevirapine metabolites were less affected by the dialysis resulting in accumulation.
Class A of Child-Pugh classification resulted in non-significant changes in nevirapine plasma levels although there exists a trend towards a progressive hepatic deterioration. For patients with Child-Pugh

class B classification, a significant prolongation of the nevirapine half-life was found, due to a significant increase in volume of distribution nevirapine, suggesting that patients with worsening hepatic function may be at risk of accumulating nevirapine in the systemic circulation.
Section 4.4. (Special Warnings and special precautions for use) of the SPC were amended to highlight that caution should be exercised when nevirapine is administered to patients with moderate hepatic dysfunction and should not be administered in-patient with severe hepatic dysfunction (see also section 5.2, Pharmacokinetic properties in adult patients).

Interactions

Considering that nevirapine is an inducer of CYP3A and potentially CYP2B6, with maximal induction occurring within 2-4 weeks of initiating multiple-dose therapy and that HIV patients are frequently subject to multiple therapies, potential pharmacokinetic interactions of nevirapine with either substances which are substrates of these isozymes or other medications frequently co-administered with antiretrovirals compounds were investigated. The main findings are summarised below:

Medicinal products with the same indication:

Nucleoside analogues

On the basis of pooled data collected from two studies BI1009 and BI834, in which 33 HIV-1-infected patients received nevirapine 400 mg/day either alone or in combination with 200-300 mg/day ddI or 0.375 to 0.75 mg/day zalcitabine (ddC) on a background of ZDV therapy, nevirapine produced a non-significant decline of 13 % in ZDV AUC and a non-significant increase of 5.8 % in ZDV C_{max}. In a subset group of 6 patients who were administered nevirapine 400 mg/day and ddI on a background of ZDV therapy, nevirapine produced a significant decline of 32% in ZDV AUC and a non-significant decline of 27 % in ZDV C_{max}. Paired data suggested that ZDV had no effect on the pharmacokinetics of nevirapine. In one crossover study, nevirapine had no effect on the steady-state pharmacokinetics of either ddI or ddC. No dose adjustment of nevirapine and nucleoside analogues is therefore considered necessary when nevirapine used with ddI, ddC and/or ZDV.

Interaction studies with lamivudine and stavudine were ongoing at the time of the granting of the Marketing Authorisation. A population pharmacokinetic study was later submitted which showed that no dosage adjustment was necessary for lamivudine when concommitantly used with nevirapine.
Results from another study in HIV infected patients (n = 25) who were administered nevirapine, nelfinavir (750 mg t.i.d.) and stavudine (30-40 mg b.i.d.) for 36 days showed no statistically significant changes in the AUC or C_{max} of stavudine.

Protease inhibitors

Since protease inhibitors are also metabolised by CYP3A, it is not excluded that co-administration with nevirapine results in an alteration in the plasma concentration of either agent.

Results from a clinical trial involving 25 HIV-infected patients administered nevirapine and indinavir (800 mg t.i.d) indicated that their co-administration leads to a 28 % mean decrease ($p < 0.01$) in indinavir AUC and no significant change in nevirapine plasma levels. No definitive clinical conclusions have been reached regarding the potential impact of co-administration of nevirapine and indinavir and therefore further data from a prospective study to address this point are required.

The combination of nevirapine and ritonavir (600 mg b.i.d using a gradual dose escalation regimen) studied in 25 HIV infected patients, did not result in any significant changes in the pharmacokinetic profile of either product.

Results from a clinical trial carried out in 31 HIV infected patients receiving nevirapine and saquinavir (hard gelatin capsules; 600 mg t.i.d.) indicated that their co-administration leads to a mean reduction of 24 % ($p = 0.041$) in saquinavir AUC and no significant change in nevirapine plasma levels. The reduction in saquinavir levels due to this interaction may further decrease the marginal plasma levels of saquinavir which are achieved with the hard gelatin capsule formulation. Another study (n=20) evaluated once daily dosing of saquinavir soft gel capsule (sgc) with a 100 mg dose of ritonavir. All patients concomitantly received nevirapine. The study showed that the combination of saquinavir sgc and 100 mg of ritonavir had no measurable effect on the pharmacokinetic parameters of nevirapine,

compared to historical controls. The effect of nevirapine on the pharmacokinetics of saquinavir sgc in the presence of 100 mg of ritonavir, was modest and clinically insignificant

The combination nevirapine and nelfinavir was under investigation at the time of the granting of the Marketing Authorisation. Final results from a 36-day study in HIV infected adult patients (n = 25) administered nevirapine, nelfinavir (750 mg t.i.d.) and stavudine (30 - 40 mg b.i.d.) showed no statistically significant changes in nelfinavir pharmacokinetic parameters after the addition of nevirapine (AUC +4 %, C_{max} +14 % and C_{min} -2 %).

There was no apparent change in the pharmacokinetics of lopinavir when used concomitantly with nevirapine in healthy volunteers. In single protease inhibitor experienced patients, nevirapine, used in combination with lopinavir / ritonavir 400/100 mg (3 capsules) twice daily and nucleoside analogues, provided very good virological response rates. Results from a pharmacokinetic study in paediatric patients revealed a decrease in lopinavir concentrations during nevirapine co-administration. The clinical significance of this interaction is unknown. However a dose increase of lopinavir / ritonavir to 533/133 mg (4 capsules or 6.5 ml) may be considered when used in combination with nevirapine in patients where reduced susceptibility to lopinavir / ritonavir is clinically suspected (by treatment history or laboratory evidence).

Non-nucleoside reverse transcriptase inhibitors

The results from a clinical trial (n=14) showed that steady-state pharmacokinetic parameters of nevirapine were not affected by co-administration of efavirenz. Drug levels of efavirenz were significantly reduced in the presence of nevirapine however. Co-administration of 400 mg nevirapine once daily with 600 mg efavirenz once daily resulted in a decrease in the AUC and Cmin of efavirenz by 22% and 36% respectively. When co-administered with nevirapine a dose increase of efavirenz to 800 mg once daily may be warranted.

Other medicinal products:

Information on potential interaction between nevirapine and CYP450 isozymes inducers and inhibitors derived from retrospective analysis of data from different clinical trials and further studies to address the potential interactions observed have been requested.

In vitro, ketoconazole was shown to significantly inhibit the formation of nevirapine-hydroxylated metabolites. In one study, administration of nevirapine 200 mg b.i.d. with ketoconazole 400 mg q.d. resulted in a significant reduction (63 % median reduction in ketoconazole AUC and a 40 % median reduction in ketoconazole C_{max}). In the same study, ketoconazole administration resulted in a 15-28 % increase in the plasma levels of nevirapine compared to historical controls. Ketoconazole and nevirapine should therefore not be given concomitantly.

Pharmacokinetic analysis in 19 patients showed that during co-administration of fluconazole and nevirapine, there was no clinically relevant effect of nevirapine on fluconazole. There was a decrease of nearly 50% in nevirapine clearance at steady state and resultant doubling nevirapine exposure. Because of greater exposure to nevirapine experienced by patients taking Viramune with fluconazole, caution should be exercised if the drugs are given concomitantly.

Nevirapine steady-state trough plasma concentration appeared to increase by 7 % with concomitant administration of cimetidine, and by 10.8 % with macrolide antibiotics, known inhibitors of CYP3A.

In vitro, rifabutin and rifampicin did not affect the formation of nevirapine-hydroxylated metabolites. Further data submitted did not support any specific dose adjustment on either nevirapine or rifampicin to increase nevirapine plasma levels to optimal therapeutic concentration. In addition it was shown that nevirapine co-administrated with rifampicin did not significantly impact on the pharmacokinetics of the active metabolite of rifampicin (25 desacetyl rifampicin). During the post-marketing phase, an other study showed that nevirapine in combination with rifabutin resulted in a significant 20 % increase in the C_{maxss}. Non-significant changes were found on 25-O-desacetyl-rifabutin (rifabutin active metabolite) AUC, C_{minss} or $C_{maxss.}$ This study suggested that there is no clinically relevant interaction between nevirapine and rifabutin.

In the framework of the third annual reassessment for Viramune, the CPMP assessed some clinical and laboratory data based on publications and one simulation of plasma nevirapine concentrations on steady state in the presence of rifampicin 600 mg QD.
In a study (Am J Respir Crit Care Med 154 (5), 1462-1467 (1996)), 298 patients with newly diagnosed pulmonary tuberculosis were randomised to receive rifabutin or rifampicin on continuation phase. The efficacy and the safety of regimens with rifabutin or rifampicin were similar. This study involved patients with newly diagnosed uncomplicated pulmonary tuberculosis, which is not the frequent situation on HIV-1 infected patients.
Two studies (J Antimycobacterial Chemother 42 (5), 621-628 (1998), abstract and J Formosan Med assoc 99 (5), 408-411 (2000), abstract) showed that in analysed clinical isolates the resistance to rifampicin was more frequent. Nevertheless the cross resistance was also frequent.
A small clinical study (Recenti Prog Med 90 (5), 254-257 (1999), abstract) involved 25 patients with a heterogeneous population (HIV, infection, multidrug-resistant, chronic liver disease). Two cases of leukopenia were found. The results were satisfactory according to the authors.
The revised CDC recommendations have been published in 1998 (MMWR 47 (RR-20), 1-58 (1998), abstract). On these principles was stated that the concomitant use of rifampicin and protease inhibitors or NNRTIs is contraindicated. The given alternative was rifabutin provided that an assessment of the patient's response is made to decide the appropriate duration of the therapy (i.e. 6 months *versus* 9 months).
Twenty-five HIV-infected patients with tuberculosis treated with highly active antiretroviral therapy (HAART) were enrolled in a study (Clin Infect Dis 30 (5), 779-783 (2000), abstract). The use of rifabutin did not apparently affect the results of the HAART on HIV infection and all 25 patients became culture-negative in 2 months.
A modelling presented by the MAH showed that nevirapine plasma levels in the presence of rifampicin 600mg QD were not stable and even with 600mg of nevirapine daily the steady state concentrations were not enough to predict efficacy.
The concomitant use of rifampicin and nevirapine has been contra-indicated. Physicians needing to treat patients co-infected with tuberculosis and using a nevirapine-containing regimen were advised to consider the use of rifabutin instead. Rifabutin and nevirapine can be administered concurrently without dose adjustments (see section 4.5. of the SPC).

In vitro data derived from studies using human liver microsomes did not reveal any effect on nevirapine hydroxylated metabolites formation when nevirapine was co-administered with dapsone, or trimetroprime/sulfamethoxazole.

No data were available on the potential interaction between nevirapine and oral contraceptives at the time of the marketing authorisation. Results from an open label study became however available during the post-marketing phase. Concomitant administration of nevirapine with a single dose of an oral contraceptive containing 0.035 ethinyl estradiol (EE) and 1 mg norethindrone (NET) in HIV infected women resulted in a significant 29% (median) reduction in the AUC of EE after 28 days of nevirapine dosing, in a significant reduction in EE mean residence time and T1/2. There was also a significant 18% reduction in the AUC of NET. The magnitude of the pharmacokinetic interaction seemed to be clinically relevant. As the oral contraceptives should not be used as the primary contraceptive in HIV infected patients, the results of the study suggested that the dose of oral contraceptive should be adjusted to allow adequate treatment for other indications like endometriosis or feminisation.

Nevirapine was capable *in vitro* of inhibiting 10-hydroxylation of warfarin (CYP3A4) although nevirapine is primarily an inducer of cytochrome P450 3A4 and 2B6 enzymes.
Warfarin elimination is almost entirely by metabolism. As increased or decreased warfarin levels are a matter of concern due to adverse events or clinical efficacy respectively, a reference to an interaction possibility was considered to be useful in the SPC.
Appropriate recommendations have been inserted into the SPC to reflect these results and as previously mentioned further investigations are necessary to clarify some of the effects observed. Since HIV infected patients are frequently subject to multiple therapies, it was recommended to address other possible significant interactions, such as antivirals, hepatotoxic medicinal products, and antibiotics.

Further to the publication, during the post-marketing phase, of results from a clinical study in healthy volunteers showing a significant reduction of indinavir plasma concentrations when co-administered with St John's wort (*Hypericum perforatum*), the CPMP considered that this interaction was also applicable to other protease inhibitors and non nucleoside reverse transcriptase inhibitors considering the same metabolism pathway of these substances as indinavir. The interaction seems to involve two different mechanisms: an induction of the metabolism by the cytochrome P450 isoenzyme 3A4 and the P-glycoprotein transporter. Since it may result in the loss of therapeutic effect and development of resistance, it was agreed to contraindicate the use of St John's wort in patients taking protease inhibitors and non-nucleoside reverse transcriptase inhibitors.

Clinical experience

Dose finding studies

Adults

In an attempt to achieve adequate levels of nevirapine *in vivo*, two dose ranging studies were carried out. The first study BI 744 (ACTG 164) used nevirapine in monotherapy whereas study BI 834 (ACTG 168) used nevirapine in combination with ZDV. Both studies used p24 antigen assays as measurement of antiretroviral activity of nevirapine.

Results from the open label study BI 744 involving 52 patients pretreated by nucleoside analogues showed that although each dose tested of nevirapine suppressed viral replication *in vitro* (dose range 12.5-600 mg/day), only 400 mg daily was able to maintain reduction during the 24 weeks after initial decline of p24 immune complex dissociation (ICD). However all the doses failed to maintain a sustained increase in CD4 cell counts after initial increase. Based on the observations that the introduction of 400 mg daily after exposure to lower doses of nevirapine reduced rash severity and incidence, one of the major dose-related effects, it was suggested to adopt the lead-in dosage regimen: 200 mg per day during two weeks prior to dose escalation.

Study BI 834 involved 83 patients who received doses of nevirapine ranging from 12.5 to 600 mg daily (2 weeks lead-in period for high doses) together with 600 mg ZDV. Results did not demonstrate any significant difference in dose response between 200 and 400 mg/day doses and 600 mg was precluded due to tolerance problem. Although these studies used p24 antigen assay which has not been demonstrated as an effective biological marker for HIV disease progression compared to plasma HIV-RNA assay, and involved a limited number of patients, the recommended posology was 400 mg/day. This recommended dose was found to be the maximal effective dose with acceptable toxicity. The once daily versus twice daily regimen of nevirapine should be further studied.

Children

The objective of the dose selection of nevirapine in children was to find adequate oral doses that could give a overall nevirapine exposure, represented by the average steady-state concentration (Css) similar to that obtained in adults given 200 mg bid (Css = 5.5 ± 2.2 µg/ml). On the basis of the model indicating that body-weight derived doses accurately predict the plasma levels measured, it was suggested to use a body-weight dosing rather than body surface dosing area used in clinical trials.

Although there are no dramatic physiologic changes at the age of 8 years old, the analysis of BSA and BW adjusted clearance suggest 8 years old as a cut-off for administration of a higher-level dose in younger children. Additional clinical studies are ongoing utilising the proposed dose regimens to support the dosage recommendations.

The choice for 7 mg/kg bid dose would result in a slight increase above the levels reported in adults. This was considered acceptable taking into account that the higher dose will help to assure adequate plasma concentrations considering the higher viral load in children than in adult patients. The safety data with this dosage is very limited and the large clinical study using nevirapine as part of combination therapy used lower dosage (120 mg/m^2).

Based on adult experience, a comparable lead-in period of two weeks was suggested for paediatric population. A 4 mg/kg dose is proposed for all children regardless the age. Although no particular study has been performed to find the optimal lead-in dose, this dose was considered acceptable considering the enzyme induction to achieve initial antiretroviral activity.

The final recommended doses for the different ages are therefore the following:

- Patients from 2 months to 8 years, 4 mg/kg once daily for 2 weeks followed by 7 mg/kg bid
- Patients from 8 years to 16 years are 4 mg/kg once daily followed by 4-mg/kg bids.

Comparative studies

Adults

In order to assess the clinical efficacy of nevirapine, five clinical trials were performed including a supportive clinical study. Most of the efficacy data derived from clinical trials using nevirapine in combination therapy with nucleoside analogues in both naive and antiretroviral experienced patients.

Since nevirapine monotherapy resulted in a short duration of the response and in a rapid emergence of resistance mainly due to a single mutation at codon 181, nevirapine should not be used in monotherapy. Data from clinical trials using nevirapine monotherapy were therefore of no clinical relevance.

Study BI 1037, a double-blind, randomised, controlled trial involving 60 asymptomatic HIV patients with CD4 cell counts between 200-500 mm^3 aimed to investigate the efficacy of nevirapine in combination with ZDV versus ZDV alone. Patients pretreated with ZDV for a duration of 0.5- 24 months (mean: 8 months) at a dose between 500 and 600 mg/day received over 28 weeks nevirapine at the dose of 200 mg/day for the first 2 weeks followed by 400 mg/day. The efficacy was evaluated based on change in viral load as measured by HIV-RNA PCR technique and quantitative HIV-1 RNA PBMC (peripheral blood mononuclear cells) microculture and change in CD4 cell counts. Results showed an initial decrease from baseline in HIV RNA greater than 1.5-log10 copies/ml in the nevirapine/ZDV arm compared to ZDV arm. However values of HIV-RNA after 12 weeks returned to baseline and no significant difference between both groups was evident. With respect to CD4 cell counts, the median change from baseline over time revealed a significant difference ($p < 0.001$) in nevirapine/ZDV group (+21.93 %) when compared to ZDV group (-24.48 %) over the 28 weeks period. The study involved a small number of patients and did not indicate any clinical benefit with the addition of nevirapine in patients taking ZDV.

Study BI 1011, an open comparative, randomised trial involving 49 HIV-infected patients with CD4 cell counts less than 500 mm^3 aimed to investigate the efficacy of nevirapine in combination with ZDV versus ZDV alone. Patients pretreated for at least 6 months with ZDV at a dose between 500 and 600 mg/day received over 28 weeks nevirapine at the dose of 200 mg/day for the first 2 weeks followed by 400 mg/day. As for the above-mentioned study, results did not show significant advantage of the combination nevirapine/ZDV over ZDV alone. Only the reduction in p24 antigen persisted after 12 weeks. However this parameter is less reliable as a marker of viral activity as compared to HIV-RNA. The same remarks as for the above-mentioned study can apply.

Study BI 1031 (ACTG 241) was a double blind, randomised, controlled trial comparing the efficacy of nevirapine/ZDV/ddI therapy versus ZDV/ddI on a large group of HIV-1 infected patients (n = 398) with prior treatment with nucleoside analogues for at least 6 months and CD4 cell counts less than 350 cells/ mm^3. Nevirapine was administered at the dose of 200 mg/day during the first two weeks followed by 200 mg twice daily. ZDV was administered at the dose of 200 mg t.i.d and ddI 200 mg twice daily (or 125 mg if weight less than 60 kg). The efficacy was evaluated based on changes in viral load and CD4 cell counts. Clinical endpoints were also evaluated in terms of time to disease progression and/or death. The study period was 48 weeks and the mean duration to nevirapine exposure was 8.8 months. Results at week 40-48 demonstrated a significant mean change from baseline in viral load as measured by HIV-RNA PCR in the nevirapine/ZDV/ddI group compared to ZDV/ddI group (reduction of 0.14 log_{10} versus increase of 0.11 log_{10} copies/ml respectively;
$p = 0.024$). Similarly, changes in CD4 cell counts over that period of time were statistically significant in favour of the nevirapine treatment group with an increase of 5 cells/ mm^3 compared to a decrease of 15 cells/ mm^3 respectively. Subgroup efficacy analysis was performed and revealed that patients with CD4 cell counts between 50-200 cells/ mm^3 had a sustained response in both changes in viral load and CD4 cell counts while treated with triple therapy compared to double therapy where patients failed this objective. Subgroup efficacy analysis in a group of 123 patients pre-treated with ZDV alone showed that the addition to ZDV of the combination nevirapine/ddI was more favourable in both HIV-RNA

reduction and CD4 cell counts increase than the addition of ddI alone. Prevention of resistance to nevirapine by the additional effect of ddI was suggested.

Results from the study did not however reveal any significant difference in terms of disease progression and/or death between both treatment groups (16 % versus 14 % respectively).

Overall, based on change in biological markers, this study demonstrated the advantage of triple therapy (nevirapine/ZDV/ddI) over double therapy (ZDV/ddI) in patients with advanced HIV-infection.

BI 1046 (INCAS trial), a randomised, double blind, controlled trial was designed to compare nevirapine/ZDV versus ZDV/ddI versus nevirapine/ZDV/ddI in 151 naive HIV patients with CD4 ranging 200-600 cells/ mm^3. Dosage regimens were similar to the ones in the previously described study BI 1031. With respect to the baseline characteristics of the population involved, the mean viral RNA was 4.41 log_{10} copies/ml. Primary endpoints were change in viral load as measured by HIV-RNA PCR (limit of detection equivalent to 20 copies/ml) and change in CD4 cell counts. Other endpoints included new AIDS defining events or selected disease recurrence and resistance emergence. The main exposure duration to nevirapine was 8.4 months. Results demonstrated a significant decrease in viral load from baseline to week 40 to 52 in nevirapine/ZDV/ddI group over the ZDV/ddI group (1.91 versus 1.35 log_{10} copies/ml respectively; $p = 0.021$).

At 24 and 52 weeks, 73 % and 57 % of patients in the triple therapy group, respectively had viral load reductions which were < 400 copies/ml. RNA levels were below the limit of detection of the ultradirect assay (<20 copies/ml) for every timepoint between weeks 40 and 52 in 45 % (or 18/40) patients of the triple therapy arm compared to 6 % (or 2/36) in ZDV/ddI arm and 0 % (or 0/28) in nevirapine/ZDV arm ($p < 0.0001$). The difference in terms of CD4 cell counts increase was also statistically significant in favour of the triple therapy group (139 versus 87 cells/ mm^3 in ZDV/ddI group; $p = 0.029$). With respect to secondary endpoints, results showed a significant clinical benefit in terms of HIV progression events with the triple therapy (12 % versus 23 % in ZDV/ddI group versus 26 % in nevirapine/ZDV group). Phenotypic resistance to nevirapine was less frequently observed in the triple therapy group (21 % of the 24 samples submitted) as compared to the nevirapine/ZDV group (69 % of the 16 samples submitted). Overall the results were not favourable to the use of nevirapine in double therapy in naive patients.

BI 1045 (ACTG 193a) was a randomised, double blind, comparative trial involving 1298 antiretroviral naive or experienced HIV-1 infected patients with CD4 cell counts less than 50 mm^3. The primary clinical endpoint was disease progression and death. Treatment groups were nevirapine/ZDV/ddI, ZDV/ddI, ZDV/ddC and ZDV/ddI alternating and the study period was 104 weeks. Doses administered were 200 mg/day of nevirapine during 4 weeks followed by 200 mg twice daily, 200 mg t.i.d of ZDV, 200 mg b.i.d of ddI and 0.75 mg t.i.d of ddC. The median time to disease progression event or death was 81.7 weeks for nevirapine/ZDV/ddI group and 62.4 weeks for ZDV/ddI group ($p = 0.061$). The difference in estimated reduction in risk of disease progression or death was significant between the triple therapy arm compared to ZDV/ddI arm (44 % versus 34 % respectively; $p = 0.0065$). The clinical benefit of the triple combination therapy was mostly apparent in experienced patients. At weeks 16, 24 and 32 the average increase of CD4 cell counts was significantly superior in the triple therapy group over ZDV/ddI group. This study confirmed the clinical benefit of the triple combination over ZDV/ddI measured as disease progression or death in patients with CD4 cell counts below 50 mm^3.

Supportive data

The potential clinical benefit of nevirapine in combination with protease inhibitors was not established nor the potential use of nevirapine in patients who failed therapy with protease inhibitors at the time of the granting of the Marketing Authorisation. Provision of data on these issues was part of the obligations to be fulfilled by the applicant. Similarly data on the response of patients who failed treatment with Viramune in triple therapy who have been treated subsequently with protease inhibitor combination therapy were to be provided.

Results from retrospective study submitted as part of the annual re-assessment of the benefit/risk profile showed that nevirapine in combination with nucleoside analogues therapy did not render patients unresponsive to subsequent protease inhibitor therapy. Further data are, however, still awaited.

Information related to study ISS047, which enrolled 68 antiretroviral naive adult patients administered either ZDV + ddI + nevirapine (n = 32) or ZDV + ddI + placebo was provided. Results showed a better response of the triple therapy on CD4 cell counts and viral load than the double therapy. The safety results from this study were in accordance with previous studies. Preliminary results from the Atlantic study were provided showing that there is no significant difference between the three regimens on short-tem evaluation (24 weeks). This study is an ongoing open-label study comparing two protease inhibitors sparing antiretroviral strategies (stavudine/ddI/lamivudine and stavudine/ddI/nevirapine) versus a standard protease inhibitor containing regimen (stavudine/ddI/indinavir) in HIV-1 infected antiretroviral naive patients with CD4 cell counts over 200 cells/mm^3 and plasma HIV RNA > 500 copies/ml. The planned duration of this study is 72 weeks.

Children

The potential clinical benefit of nevirapine was not established in children at the time of the granting of the Marketing Authorisation but submission of a paediatric dossier was part of the obligations to be fulfilled by the applicant.

The extension of the indication of nevirapine to children is mainly based on the extrapolation of data obtained from adult patients. In addition, specific studies have been performed to define dosage recommendation of nevirapine on the basis of pharmacokinetics and biological efficacy on surrogate markers and to confirm the safety of nevirapine in this population. All the clinical trials have been performed according to GCP standards and agreed international ethical principles. The majority of patients received nevirapine suspension. Patients were however allowed to take nevirapine tablets based on a patient's dose and ability to swallow tablets.

The clinical programme consisted of 4 clinical trials, BI 1100.882, 1100.892, 1100.859 (expanded access trial) and the double blind ACTG 245 (1100.1032). Most of the data provided refer to safety.

An overview of the design of the studies are given in the table below:

Study Number	Design	Study Regimen	Dose	Intended Study Duration	Number of patients (as of cut-off date)/prior nucleoside status Male/Female Mean age years (range)
Completed studies					
1100.882 (ACTG 180)	Open label Multicenter	• NVP (11) • NVP/ZDV (17 patients) • NVP/ZDV /ddI (9 patients)	120 mg/m2 q.d. during 28 days followed by 120 mg/m^2 bid (patients > 9 years old) or 200 mg/m^2 (patients < 9 years old)	6 months	37 children/naive and experienced 20 M/17 F 3.3 (0.17 – 15.1)
ACTG 245 (1100.1032)	Randomised Double blind Placebo-controlled	• NVP/ZDV /ddI • ZDV/ddI • NVP/ddI	• 120mg/m^2 qd/x14d then 120mg/m^2 bid	48 weeks plus extension	431 children[2] (305 nevirapine treated) experienced children with advanced HIV infection 254 M/177 F 7.5 (0.8 – 19.3)
Ongoing studies					
1100.859	Open-label expanded access	NVP NVP with other antiretrovirals	NVP 120mg/m^2x14d then 120 mg/m^2 bid	Until IND is withdrawn or nevirapine becomes registered	19 children naive and experienced 5 M/13 F (gender not available for one) 2 (3 days-11 years)

Study Number	Design	Study Regimen	Dose	Intended Study Duration	Number of patients (as of cut-off date)/prior nucleoside status Male/Female Mean age years (range)
1100.892	Open-label long term nevirapine access	• NVP • NVP/ZDV • NVP/ZDV /ddI	240 mg/m2 or 400 mg/m2	Until IND is withdrawn or nevirapine becomes registered	29[3] children experienced 16 M/13 F 4.4 (0.8 –15.6)
Clinical pharmacology studies					
1100.853 (ACTG 165)	Single dose pharmacokinetic	Nevirapine		Single dose + 4 days follow-up	9 HIV infected children

[1] Initiation = date of first patient enrolled; completion date not yet defined for ongoing studies

[2] 432 patients were enrolled; however one patient discontinued the trial before medication was administered and only demography data are available for this patient.

[3] These patients previously participated in trial 1100.882

Study 1100.882

Efficacy was measured in terms of virologic, immunologic and growth activity markers using median changes from baseline. Virologic response to therapy was measured by HIV RNA using a test with a limit of quantification of 400 copies/ml. Differences among groups were not tested because dose cohorts were not randomised. The protocol of this study has been amended to reflect the changes to standard of care.

Patients treated with nevirapine/zidovudine/didanosine (n = 8) maintained a median decrease of greater than 2 logs below baseline in HIV RNA levels for 8 weeks (7 of 8 achieved a nadir of at least 1.6 logs) with results maintaining statistically significantly below baseline through 24-28 weeks (p = 0.03). Only one of eight patients treated with triple therapy had HIV RNA levels that returned to baseline by the end of the study. Triple therapy increased the percent of CD4 cells and significantly increased the weight-age index for triple therapy patients. The HIV RNA levels for two patients receiving triple therapy in this trial became undetectable (< 20 copies/ml). These two patients lost HIV antibody, suggesting that suppression of viral replication was nearly complete. Patients in all three treatment regimens maintained a median increase above baseline in percent CD4 cells for 24 to 32 weeks.

Results on HIV RNA levels, p24 antigen levels, CD4 cells and weight growth-index suggested that treatment with triple therapy gives more consistent improvement

Results obtained with double therapy and monotherapy do not support the use of any of these regimens. Although limited to a small group of patients the data provided indicate that combination antiretroviral therapy including could have a potent and prolonged activity.

Study ACTG 245

Results of the study ACTG 245, which involved children and adolescents with advanced disease and previous antiviral therapy were not available at the time of recommendation for the granting of a marketing authorisation. Data from ACTG 245 were submitted later as part of the specific obligations to be fulfilled post –authorisation. The antiretroviral activity was measured by the reduction in plasma HIV RNA and plasma p24 antigen levels at 48 weeks. Safety and pharmacokinetics were also evaluated. Triple therapy appeared to have the most favourable drop in HIV RNA from baseline at almost all time points (4, 12, 24, 36 and 48 weeks), followed by the didanosine/zidovudine arm. The reduction observed in the triple therapy arm exceeded that observed with didanosine/zidovudine ($p=0.035$) and with didanosine/nevirapine ($p<0.00001$). There were no major differences in adverse reactions between the different arms. Pharmacokinetic parameters were found to be in accordance with previous studies. The most important limitation of the of the ACTG 245 study was the nevirapine dosage. A significant number of patients were treated with a lower dosage (120 mg/m^2) than the regimen proposed in the SPC. This fact has implications on safety and probably efficacy results.It was accepted from the beginning for Viramune Oral formulation that, in the absence of extensive data from paediatric clinical trials, the goal in children should be to achieve nevirapine steady state plasma levels

similar to the ones detected in adult clinical trials, i.e. 4 to 6 μg/ml (median plasma steady state of 5.3μg/ml), using 200mg b.i.d. This solution was accepted even knowing that markers of immunologic function, virus load, and rates of disease progression are associated with age.

Evaluation of data, mainly from study ACTG 245, suggests that a dose based on body surface area rather than body weight is probably a better therapeutic regimen to achieve a nevirapine steady state plasma levels similar to the adults. In fact the combined study results showed that the mg/kg dose requirements decline with the age and the dosing requirements based on body surface area remain reasonably constant with age when body surface area exceeds 0.3 m^2. The surface area basis that mirrors the physiological development of the paediatric patient seems to be more appropriate to guide the nevirapine dose regimen.

The data from ACTG 245 study also suggests that 150mg/m^2 BID may be a more suitable dose regimen to achieve the proposed goal (median plasma steady state of 5.3μg/ml) as the dose of 120mg/m^2 BID used in the ACTG 245 and other studies would result in an average exposure of 4.3μg/ml.

Prevention of perinatal transmission

During the post-authorisation phase, results from a HIVNET 012, a randomised double blind Phase III clinical study carried out in Uganda showed that the nevirapine therapy (200 mg dose orally in labour and 2 mg/kg to her infant within 72 h after birth) significantly reduced the risk of perinatal transmission in HIV infected pregnant women during the first 14 weeks compared with ZDV regimen (600 mg at the onset of labour and 300 mg every 3 hours until delivery, and 4 mg/kg twice daily to babies for 7 days). The cumulative HIV-1 infant infection rate at 14-16 weeks was 13.1 % (n = 310) in the nevirapine group, versus 25.1 % (n = 308) in the ultra-short zidovudine group (p = 0.00063).

PACTG 316 (1100.1207) was an international study performed in North and South America, Europe and the West Indies. The study was a placebo controlled, randomised study planned to investigate the use of the HIVNET 012 nevirapine regimen in HIV-1 positive pregnant women of ≥ 28 weeks gestation. The study medication was given in addition to whatever additional antiretroviral treatment has been prescribed for the mother and child. The infants were followed up for the first six months of life. The main objective was to evaluate the effect of the regimen on the incidence of HIV infection, the safety of the regimen for the mothers and infants, the relationship between maternal viral load at delivery and HIV transmission and the effect of nevirapine treatment on HIV RNA levels in infants who are determined to be HIV infected. The target recruitment was 2009 mother infant pairs. The recruitment was halted in June 2000, after 1506 women being recruited (1174 received study treatment and had infants with known HIV status at the time of the analysis), because the initial objective (50% decrease in vertical transmission) could not be met due to the very low vertical transmission observed in the trial (1.5%; 95% confidence interval 1.0-27%).
The SAINT study (1100.1287) compared the efficacy of two regimens in the prevention of vertical transmission of HIV in South Africa. It is a randomised, open label study which compared a nevirapine regimen (200 mg nevirapine to the mother during active labour and 6 mg to the infant between 24 and 48 hours post delivery) with a short course zidovudine + lamivudine regimen (the mother receives 600 mg zidovudine initially and then 300 mg every 3 hours during labour and 300mg BID for 7 days post delivery plus lamivudine 150 mg BID during labour and for 7 days post delivery; the infant receives zidovudine 12 mg BID (4 mg/kg BID if weight < 2 kg) for 7 days plus lamivudine 6 mg BID (2 mg/kg BID if weight <2 kg) for 7 days. Mothers and infants were followed for the first 6-12 weeks of life. The primary objective was to evaluate the efficacy of nevirapine versus zidovudine + lamivudine in reducing peripartum mother to child HIV transmission of HIV. The secondary objective was to evaluate the safety and tolerance of the two regimens in both the mothers and infants. The target enrolment was 1350 mothers. Recruitment commenced in April 1999. Results of a primary analysis of the incidence of peripartum infections (intrapartum and post-partum up to ten weeks) were presented.

The analysis performed (Kaplan-Meier) estimates of HIV transmission rates were 12.7% for NVP and 9.5% for AZT+lamivudine arms. Although there was a trend favourable to AZT+lamivudine there are no significant differences between the arms.

The efficacy results showed no significant difference in HIV-1 transmission rates through 6 to 8 weeks between the nevirapine group (5.7 %, n = 652) and the zidovudine plus lamivudine group (3.6 %, n = 649). The rate of adverse events was similar in both groups. There was greater risk of HIV-1 transmission to babies whose mothers received their nevirapine or their zidovudine plus lamivudine doses less than 2 hours before delivery. The secondary analysis on resistance showed that 68% of nevirapine-exposed mothers of this study had resistant strains at approximately 4 weeks after delivery.

The clinical relevance of these data in European populations has not been established. Furthermore, in the case nevirapine is used, as single dose to prevent vertical transmission of HIV-1 infection, the risk of hepatotoxicity in mother and child cannot be excluded.

Virological data derived from clinical isolates

Limited evaluation of resistance development was carried out. Rapid emergence of nevirapine resistant virus, in particularly during nevirapine monotherapy, was observed with loss of antiviral activity (100 to 250-fold). Phenotypic and genetypic changes occurred in HIV isolates from patients treated with nevirapine monotherapy or in combination with ZDV over 1 to 12 weeks. By week 8 of nevirapine monotherapy 100 % of the patients had HIV isolates with more than 100-fold decrease in susceptibility to nevirapine regardless of dose.

Studies to evaluate the genetic analysis of resistant mutants were carried out in 6 ZDV-experienced adult patients and 4 antiretroviral-naive paediatric patients, who received combination regimens with ZDV, nevirapine or ddI. Genotypes of cloned RT genes were determined in sequential clinical isolates before and after receiving nevirapine therapy. Data indicated that resistance to nevirapine could be attributed to single-based pair mutations of the RT gene located at the nevirapine binding sites i.e. changes in amino acid residues 103, 106, 108, 181, 188 and 190, in all treatment regimens examined. The pattern of mutations arising appeared to be influenced by prior and current drug therapy. Mutation at position 181, which is the most frequent mutation, was found to suppress ZDV resistance conferred by mutations 41 and 215.

Multiple mutations from the nevirapine binding pocket result in high level resistance to nevirapine. All the mutations that considerably changed susceptibilities to nevirapine, i.e. at position 181 (substitution from of cysteine for tyrosine), 190 and 238 had little or no effect on the susceptibilities to ZDV or ddI.

Phenotypic resistance to nevirapine was less observed in triple therapy group, where a majority of patients maintained viral load beneath the limit of quantification, (21 %, 5 of the 24 samples submitted) than in double therapy, nevirapine/ZDV group (69 % of the 16 samples submitted) in study BI 1046.

Overall HIV-1 resistance to nevirapine is rapidly developed when nevirapine is used either in monotherapy or double therapy with ZDV as compared to triple therapy. The clinical relevance of phenotypic and genotypic changes associated with nevirapine has not been established.

Data obtained from study PACTG 316 showed that nevirapine resistance mutations could emerge after a single dose, also in women on other ARV therapy. Mutations associated to nevirapine resistance were found in 2.3% of the women at delivery. Of the 95 women who received intrapartum nevirapine, 15% developed nevirapine resistance mutations at 6 weeks post partum. No correlation was found between the nevirapine resistance and CD4 cell counts, HIV RNA copy number or background antiretroviral therapy

The objective of a retrospective cohort study ("Non-nuceloside reverse transcriptase inhibitor [NNRTI] resistance among patients failing a nevirapine plus protease inhibitor-containing regimen") was to determine the rate of nevirapine resistance in patients failing a nevirapine (NVP) plus protease inhibitor (PI) based regimen, and whether these isolates remain susceptible to other NNRTI. Eighty-eight HIV-infected, NNRTI-naïve patients receiving NVP plus PI as a rescue regimen after PI treatment failure were involved in the study. A baseline resistance of 70% to NVP, 91% to efavirenz and 71% to delavirdine was found. At 24 weeks the resistance to NVP was found in 92% of the patients. The development of NVP resistance was associated to the baseline PI resistance included on the regimen.

Cross-resistance

A study conducted in France was "449 Resistance profile and cross-resistance to HIV-1 among 104 patients failing a NNRTI containing regimen". The objective of this study was to determine the resistance profile and the rate of cross-resistance in patients failing efavirenz or a NVP and that efavirenz-containing regimen and to investigate whether ZDV or other thymidine analog nucleosides lead to a particular genotypic pattern in NVP-failing patients. One hundred percent of the isolates from patients failing efavirenz showed cross-resistance to NVP and almost 100% of the patients treated with nevirapine showed NNRTI resistance pattern. Eighty percent of the isolates from patients who fail NVP treatment and presenting NNRTIs resistance profiles harboured mutations conferring cross-resistance to efavirenz and 9% mutations conferring resistance to NVP alone. Patients who failed consecutively NVP and efavirenz therapy showed resistance to all NNRTIs. When ZDV or stavudine were used in the regimen the isolates were more frequently resistant to efavirenz.

As requested by the Committee, further investigation on the development of resistance to nevirapine and where appropriate to other antiretroviral agents in Viramune failed patients will be carried out in ongoing and future studies. Further phenotypic and genotypic resistance data derived from the INCAS study were submitted. Genotypic and phenotypic resistance was examined for patients receiving nevirapine in triple and double therapy drug combination therapy, and in the non-nevirapine comparative group from the INCAS study. Of the three study groups (nevirapine/ZDV, ZDV/ddI and nevirapine/ZDV/ddI), 16, 19 and 28 patients respectively had evaluable baseline isolates and subsequently remained in the study for at least 24 weeks. At baseline, there were five cases of phenotypic resistance to nevirapine; the IC_{50} values were 5 to 6.5-fold increased in three and > 100 fold in two. At 24 weeks, all available isolates recoverable from patients receiving nevirapine were resistant to this agent, while 18/21 (86 %) patients carried such isolates at 30-60 weeks. In 16 subjects viral suppression was below the limits of detection (< 20 copies/ml = 14; < 400 copies/ml = 2). Assuming that suppression below < 20 copies/ml implies nevirapine susceptibility of the virus, 45 % (17/38) of patients had virus measured or imputed to be susceptible to nevirapine. All 11 subjects receiving nevirapine + zidovudine who were tested for phenotypic resistance were resistant to nevirapine by six months. Over the entire period of observation, one case of didanosine resistance was seen. Zidovudine resistance emerged as more frequent after 30-60 weeks, especially in patients receiving double combination therapy. Based on the increase in IC_{50}, zidovudine resistance appeared lower in the nevirapine + zidovudine + didanosine group than the other treatment groups. With respect to nevirapine resistance, all isolates that were sequenced carried at least one mutation associated with resistance, the most common single changes being K103N and Y181C. Combinations of mutations were found in nine of the 12 patients observed. These data from INCAS illustrated that the use of highly active drug therapies is associated with a delay in the development of antiretroviral drug resistance.

Safety

The main safety data was obtained from the four controlled combination therapy trials (BI1037, BI1011, BI1046 and BI1031), which enrolled 906 patients with a median duration of nevirapine exposure of 11.1 months. Almost half of these patients received nevirapine for a period longer than 12 months. The overall characteristics of the population were male (86 %), white (80 %) nucleoside analogues experienced patients (60 %).

The analysis revealed that the adverse effects related to nevirapine are mostly rash, nausea, headache, abnormal liver function tests (LFTs), fatigue, fever, vomiting and myalgia. Discontinuation of nevirapine therapy was mainly due to rash (6.8 %), fever (2.9 %), abnormal LFTs (2.5 %), fatigue (2.0 %) and nausea (1.9 %).

The overall incidence of drug-related events increased when nevirapine was added to a previous antiretroviral therapy. Similarly drug related adverse events were more frequently reported when nevirapine is used in combination therapy as compared to monotherapy (38 % and 33 % respectively).

With respect to rash, data showed that 16 % of the rashes reported could be attributed to nevirapine. Five patients presented a life-threatening rash. No correlation was however found between rash incidence and nevirapine plasma levels. It was found that the greatest risk to develop rash occurred in the first 28 days of nevirapine therapy. In the majority of cases reported rash was autolimited but when associated to fever or other general symptoms rash was seen as potentially dangerous event. Evolution of rash to Stevens-Johnson syndrome (SJS) and particularly to Toxic Epidermal Necrolisis (TEN) described by Lyell (Lyell syndrome) was an ominous sign. From analysis of all available clinical data (2861 patients) nine patients had confirmed SJS (0.3 %) and two of them were felt to have a transition syndrome to TEN.

Post-marketing surveillance showed that the nature of spontaneous reports were similar to the adverse events observed in clinical trials. Overall reported incidence of these adverse events (SJS/TEN) were however lower than observed in clinical trials.

Cases of diarrhoea, vomiting, abdominal pain, bilirubinaemia and jaundice were reported in the first periodic safety update report: In addition, the most frequently reported reactions with respect to the liver and biliary system disorders were elevations of liver function tests, of which 43 % were considered serious. It was therefore considered acceptable to include into the SPC the relevant information on these undesirable effects.

Three fatal cases of Stevens-Johnson syndrome (SJS) were reported in the second Periodic Safety Update report (PSUR). It is likely that the relationship between nevirapine therapy and the onset of SJS had caused these fatalities. The inclusion of allergic reactions and rash associated with constitutional symptoms and visceral involvement was considered acceptable considering reactions related to the skin and appendages reported. The wording in the SPC had therefore been strengthening.

Liver function abnormalities (LFTs) abnormalities were expected with nevirapine mainly due to enzymatic induction. Toxic hepatitis was a non-rare complication observed in the four referred studies. Many patients experienced LFTs abnormalities other than GGT elevation (ALT and AST increases) which led to temporary or definitive interruption of nevirapine therapy. The rate of withdrawal due to hepatitis reported from clinical trials was 0.8 %. In order to prevent the development of hepatitis, a close monitoring of the liver function test abnormalities during the first weeks of nevirapine therapy is therefore recommended. The incidence of drug-related hepatitis was not higher with nevirapine than with other antiretrovirals. Post marketing surveillance data confirmed the hepatic toxicity of nevirapine. A total of eight cases of fulminant hepatitis were described in both PSURs (four cases in each one). Although the causal relationship has not been established, nevirapine seemed to have an important role in these cases. The risk of potentially fatal hepatotoxicity reactions has been strengthening in the Summary of Product Characteristics.

Several possible cases of hypersensitivity syndrome characterised by fever and rash plus alterations of liver function (including hepatitis or liver failure) or renal involvement or pancreatitis or myocaditis or haematoligical involvement (lymphoadenopathy, granulocytopaenia, atypical lymphocytosis, eosinophilia) have been found over the three PSURs. Therefore it was considered appropriate to include in the relevant sections of the SPC a warning on this effect.

Although the warnings had already been strengthened in the SPC and PL, additional cases of severe, life-threatening and sometimes fatal cutaneous (including SJS and TEN) and hepatic reactions associated with clinical and biological signs of hypersensitivity have been reported. A cumulative review of the four first PSURs and the assessment of these cases and further analysis from large clinical studies and spontaneous reports database showed that severe and life-threatening skin reactions, including fatal cases, occur mainly during the first 6 weeks of nevirapine therapy. Some risk factors of severity have been identified: these are the non-respect of the lead-in dose escalation regimen and a delay in seeking medical attention when the first symptoms appear. Some of them were associated with signs of hypersensitivity (characterised by rash, and constitutional symptoms such as fever, arthralgia, myalgia, lymphadenopathy and visceral involvement such as hepatitis, eosinophilia and renal dysfunction). A prospective, randomised, open-label trial showed that prophylactic use of prednisone to prevent rash may result in an increase of rash associated to nevirapine. With respect to the hepatic reactions, the above mentioned analysis showed that most of the cases of serious hepatitis and hepatic failure events have been reported to occur mainly within the first 8 weeks of treatment with nevirapine, during which a close monitoring is required. One third of cases have however been reported to occur after this critical period. Increased ASAT or ALAT levels prior to the start of therapy with nevirapine containing regimens are associated with greater risk of hepatic adverse reactions.

Many hepatic adverse reactions did not occur in a context of hypersensitivity syndrome, the hypersensitivity syndrome can, however, course with hepatic compromise.

Therefore having re-assessed the benefit/risk profile of nevirapine, the warnings concerning the occurrence of these events have been reinforced. In addition new recommendations for the liver and cutaneous monitoring of patients treated with nevirapine, especially during the first 8 weeks of treatment (the period of occurrence of the greatest risk of hepatic events and skin reactions has then been reassessed to be within the first 6 weeks of therapy, see Expanded analysis of Hepatic reactions in Viramune clinical trials) or when the patients experience clinical or biological signs of hepatitis or hypersensitivity, have been introduced through an urgent procedure.

Eighteen cases of methadone withdrawal following the concomitant administration of nevirapine, which is a known inducer of cytochrome P 450 system, have been reported. The symptoms of narcotic withdrawal appeared soon after the administration of nevirapine and required an increase in methadone dosage. A statement on the potential interaction between both products has been introduced in the SPC.

Treatment with a combination of at least three antiretroviral drugs can induce a characteristic syndrome termed lipodystrophy or fat redistribution syndrome containing peripheral fat wasting (including accentuation of facial folds) and central adiposity. Metabolic disturbances such as hyperlipidaemia and insulin resistance also often appear. PIs were originally believed to be the causal agents. NRTIs have also been implicated. In addition, lipodystrophy has also been observed with protease-inhibitor-sparing regimens. The emerging picture is that of a connection between visceral lipomatosis and protease inhibitors and lipoatrophy and NRTIs correlating with different possible mechanisms e.g. effects on lipoprotein production and adipocyte differentiation. Non-drug factors are also of importance e.g. increasing age, duration and severity of HIV infection.
Following evaluation of data submitted by all MAHs of antiretroviral medicinal products, a class labelling, which harmonises the information on lipodystrophy for all three classes of antiretroviral products, has been agreed and implemented in the product information for all antiretroviral medicinal products. The wording presents as much as possible of the presently available knowledge; it gives a description of the condition (although there is at present no clear definition of lipodystrophy), information about causality and surveillance measures. The higher risk of developing lipodystrophy with long-term therapy as well as importance of factors such as age and disease related factors is mentioned.

Expanded analysis of Hepatic reactions in Viramune clinical trials

The MAH has presented to the CPMP, a Technical Clinical Report named “Expanded Analysis of Hepatic Reactions in Viramune Clinical trials”, which overcomes some demographic limitations on gender, race and CD4+ cell counts of previous analysis [integration of Atlantic and FCT-302 into the

Integrated Summary of Safety (ISS) database and data generated from other trials]. The investigation incorporated databases from 17 clinical trials, that were performed in several countries from Europe, North and South America, Australia and Africa. A total of 2545 nevirapine treated patients were included from which 663 were women, 683 were blacks and 1137 had baseline CD4+ cell counts above 250. The main demographic characteristics of the studied population is summarised in the following tables:

Patients included in the Analysis from controlled trials			
	Nevirapine	Control	Mean exposure (weeks)
Total	1731	1911	50

Non-comparative trials from which only nevirapine data were available		
	Nevirapine (patients)	Mean exposure (weeks)
Total	643	45

The aim of this analysis was to determine the risk of hepatic events, to describe the timing and clinical presentation of these events, and to clarify the inter-relation of risk factors of hepatic reactions observed in Viramune clinical trials. In order to better understand the underlying causes and risk factors of hepatic events, this analysis tried to improve the precision of classifying hepatotoxicity by:
- Implementing a standardized process for selection and review of patients with potential symptomatic hepatic events,
- differentiating between symptomatic and asymptomatic elevations in ALT or AST,
- separating symptomatic hepatic events that were associated with rash and other potential immune symptoms from hepatic events that did not have possible immune component.

The methodology for patient capture from databases that could possibly have had a hepatic event was considered as acceptable. In an overall population of 4456 patients (nevirapine and non-nevirapine treated patients) the computer algorithms identified 536 patients as potential cases of symptomatic hepatic events, whose records were reviewed by internal and external clinical experts. Seven patients met criteria for review as both non-nevirapine controls and as open label, non-comparative nevirapine patients and hence, were reviewed in both categories.

Due to several factors as multiple disease processes involved in HIV-1 infection, poly-medication, and the degree of detail reported in clinical trial database, it was not possible to systematically distinguish between fluctuations in chronic liver disease and possible drug induced exacerbations of chronic liver disease.
At the end of the process the reviewed categories were differentiated into three situations:

a) rash-associated symptomatic hepatic events.
b) other symptomatic hepatic events.
c) asymptomatic elevations of ALT and AST > 5 x ULN.

The cut-off of 5 x ULN for ALT and AST was used since it has been used conventionally as an indicator of potential hepatic toxicity.

The main conclusions provided by the MAH and endorsed by the CPMP were as follows:
Based on the current and previous analysis (including evaluations of cohort studies and spontaneously reported cases), occurrence of “symptomatic hepatic events” attributable to Viramune varies according to the population under treatment and the clinical presentations. Moreover, hepatic events may be categorised into “Rash-associated events” and “other hepatic events”. In addition, fulminant hepatitis or death due to Viramune events is rare. Risk factors (and perhaps pathogenic mechanisms) differ for the different types of clinical presentations of hepatic events.

- Rash and associated hepatic events:

Are associated with Viramune treatment,
Occur in the first 6 weeks of therapy,
Higher baseline CD4+ cell counts increased risk,
Females were at higher risk than males,
The risk of hepatic events was similar for blacks and whites.

- Other hepatic events and asymptomatic transaminase elevations:

May be related to Viramune treatment,
Risk of these events is greatest in the first 6 weeks, but events continued to occur thereafter;
After 18 weeks, this was similar to control patients.
For both Viramune and non-Viramune patients,
Elevated baseline hepatic enzymes increased risk,
Co-infection with hepatitis B increased risk,

Co-infection with hepatitis C was a significant risk factor asymptomatic transaminase elevations, but not for other hepatic events.

- Transaminase elevations in the absence of clinical hepatitis:

Viramune therapy should be interrupted for asymptomatic transaminase elevations greater than 5xULN (patients should be evaluated for viral hepatitis and other causes of liver injury),
It is not medically prudent to re-introduce Viramune therapy in patients who have had such transaminase elevations in conjunction with rash or other symptomatic hepatic events.
However, data were too limited to make a general recommendation regarding risk/benefit of re-introduction of Viramune following return to transaminase levels to baseline, and physicians should decide how to manage the patient, on a case-by-case basis.
The other recommendations in the Viramune hepatic event management remain appropriate.

Further to the proposal of the MAH to inform prescribers of the conclusion of the post-marketing surveillance analysis and of the Viramune expanding clinical trial database, a Dear Doctor Letter has been adopted by the CPMP on 21 January 2003. This letter specifically drew on the above-summarised conclusions and on the related SPC changes the attention of prescribers.

Liver impairment in HIV positive patients

Further to the discussions held by the *Ad-hoc Group of Experts on Anti-HIV medicinal products* in November 2001, the CPMP agreed that liver impairment was of increasing concern in HIV positive patients both in the form of adverse hepatic effects in patients with normal liver function prior to antiretroviral treatment (ART) and as regards patients with chronic liver disease treated with ART.
In January 2002 the CPMP requested the MAH for all authorised anti-retroviral medicinal products to conduct a retrospective review of clinical trials and post marketing data relating to the use of their product(s) in patients with hepatic impairment and/or HBV/HCV co-infection. Following review of the submitted responses and discussions held during the CPMP meeting and the Pharmacovigilance Working Party meeting in October 2002, the CPMP adopted a list of questions (including general, product specific and SPC wording recommendations).

The review of the MAHs responses has essentially confirmed that co-infected patients and patients with underlying liver disorders are at increased risk for adverse events, essentially confined to liver events. Overall, there is a disturbing lack of general and product specific knowledge (e.g relevant pharmacokinetic data in patients with liver impairment), but there are ongoing activities.
For some of the products still undergoing drug development, the MAHs have confirmed that co-infected patients will not be excluded from participation in the studies. The CPMP stressed that whenever feasible a minimum number of co-infected patients should be included in forthcoming studies in order to provide a reasonable basis for a relevant safety (and efficacy) analysis.

Following the review of responses submitted by all MAHs of antiretroviral medicinal products, a class labelling on “liver disease” has been agreed and implemented in the product information for all antiretroviral medicinal products.

In accordance with the CPMP recommendations for all antiretroviral medicinal products to include in section 5.2, data on AUC,Cmax and Cmin (including CV), if available, derived from patients, the SPC of Viramune has been amended to include pharmacokinetic data reported in the literature . These data indicate that steady state through levels are lower than those measured earlier, and that nevirapine plasma concentrations above 3.5 μg/ml seem to be related to an acceptable efficacy level in patients treated with multiple antiretroviral agents.
The CPMP discussed the inclusion, in section 4.2 of the SPC (*Posology and Method of Administration*), of a recommendation for physicians to monitor the plasma levels in order to maintain appropriate target steady-state nevirapine trough concentrations with a cross reference to section 5.2 (*Pharmacokinetic properties*). This proposal has not been endorsed since there is at present, no convincing evidence that any minimum trough level correlates with long-term success with Viramune.

Future studies with regard to liver disease

The MAH is planning to perform a prospective Pharmacokinetic study in 60 hepatically impaired patients (trial 1100.1448). This initiative follows the CPMP recommendations, requesting MAHs to study the safety of their antiretroviral medicinal products in patients with liver impairment and hepatitis co-infection. The MAH has committed to provide the CPMP with the results of this trial as soon as available. The trial is projected to complete during the year 2004.
In addition, with respect to the request for follow-up as regards liver disorders and ART through cohort studies, the CPMP noted that the HAART oversight committee is active and will provide proposals for agreement.

Children

Patients exposure

The data of a total of 487 paediatric patients in multiple-dose trials represent the basis for detailed presentation of demographic and safety data. Of these, 361 were treated with nevirapine, (305 patients in ACTG 245, 37 in 1100.882 and 19 patients in 1100.859). Detailed exposure data are presented only for the 37 patients who participated in trial 1100.882 and 29 of these 37 patients who continued nevirapine therapy in trial 1100.892. Limited exposure data are available for 17 of the 19 patients enrolled in the expanded access trial, 1100.859. Detailed exposure data were not presented for the 305 nevirapine-treated patients in ACTG 245.

The majority of these patients were male (279/487, 57 %) aged ranging from 3 days to 19.3 years. Patients age varied among the trials: 2.0, 0.9 and 2.1 years (median age for trials 1100.859, 1100. 882 and 1100.892 respectively) and 7.5 years (mean age in ACTG 245). Forty-two percent (204/487) were black, 38 % hispanic (184/487), 19 % white (93/487), 1 % were of other races and data were not available for 3 patients (0.6 %). Because study 1100.859 was an expanded access trial, only nevirapine-related events and deaths of any causality were to be collected on case report forms. Patients mostly received nevirapine therapy at the dose of 120 mg/m^2/day for 2 weeks followed by 120 mg/m^2/bid. Few data on patients treated with 200-mg/m^2 bids are available from studies 1100.882 and 892 (n = 22).

Adverse events and serious adverse events/deaths

Based on experience of 361 paediatric patients treated in clinical trials, the most frequently reported adverse events related to nevirapine were similar to those observed in adults, with the exception of granulocytopaenia, which was more commonly observed in children

In studies 1100.882 and 892 for which all the adverse events are reported, rashes occurred in 43 % of patients. However they were considered related to nevirapine only in 16 % and all were mild. Therapy was discontinued only in one patient.

In the large trial ACTG 245, only severe adverse events are described and 11 (4 %) of the 305 patients with nevirapine experienced a rash compared to 1/126 not receiving nevirapine.

Most of these rashes occurred within the first 6 weeks of therapy as observed in adults with nevirapine related rashes. Two children (0.7 %) developed a Stevens-Johnson syndrome and 1 had an anaphylactic reaction including a rash. In adults the frequency of Steven-Johnson syndrome is 0.7 %.

No other serious adverse events appeared to occur more frequently in patients whose regimen included nevirapine in trial ACTG 245. Hepatic adverse events (frequently associated with the use of nevirapine in adults) were infrequent. Additionally to the documentation included in the initial application, the company provided the preliminary results from Study 1100.1222 (ACTG 356). In this small but relevant study a nevirapine dose similar to the one proposed in SPC was given to the patients. This trial partially overcomes the major concerns, i.e few safety data on children with the proposed therapy regimens. Although the study relies only on data from children under two years it seems acceptable to extrapolate these preliminary safety results to children until 16 years as the safety data are available for adults and the safety profile was not significantly different on both groups.

Overall nevirapine appears to be safe for use in HIV-1 infected children when given at the dose of 120-mg/m2 bids after a lead-in period of 2 weeks at 120 mg/m^2/day. However the data available on higher dosages is limited. The higher dosage proposed in younger children can be considered as safe as the dosage used in older children and adults based on the fact that pharmacokinetic evaluation indicates that the plasma concentrations in children up to 8 years with this dosage will be similar to those with 120 mg/m^2 bid in older children and 200 mg bid in adults.

5. Overall conclusions and benefit/risk assessment

Although additional information will have to be submitted with regard to chemical and pharmaceutical aspects, the data are acceptable to ensure the quality and the consistency of the tablets.
The quality of the oral suspension is considered to be satisfactory when used in accordance with the conditions defined in the SPC. Physicochemical aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

The preclinical data are extensive and demonstrated the antiviral activity of nevirapine and relevant for the indication claimed. No additional preclinical testing was considered necessary with respect to the oral suspension.

The efficacy of nevirapine in adults was established on grounds of favourable changes in plasma HIV-1 RNA levels, CD4 cell counts and clinical data. Triple combination of nevirapine/ZDV/ddI demonstrated a clinically relevant and statistically significant advantage over ZDV/ddI and in a greater extent over nevirapine/ZDV group. Results however did not favour the use of nevirapine in double therapy with one nucleoside in naive patients. The clinical benefit of nevirapine, based on the presented data, was considered favourable in triple therapy. Not all combinations with other antiretroviral medicinal products, especially with protease inhibitors, have been studied. However taking into account that the current medical practice in the management of HIV-infected patients fully advocates the combination of antiretroviral drugs, the CPMP supported the use of nevirapine in combination but requested the company to submit additional data on the use of nevirapine with different combination therapy.
Based on the data available, nevirapine was shown to have an acceptable safety profile despite the potential cutaneous and hepatic severe adverse events occasionally reported.

The overall risk benefit assessment ratio of nevirapine established in adults is favourable.

In accordance with the CPMP recommendations (CPMP Points to Consider in the assessment of New Antiretroviral Products (CPMP/602/95 rev.1), it is in principle appropriate to quantitatively extrapolate from efficacy in adults, provided that reliable pharmacokinetic data allow for proper dosage recommendations in different age group. Data on pharmacokinetics of nevirapine have been submitted allowing a paediatric dosage resulting in plasma concentrations associated with efficacy and long term tolerability in adults. Based on the pharmacokinetics model, the administration of nevirapine based on body-weight dosing was preferred. Although there are no dramatic physiologic changes at the age of 8 years old, a dosage shift at this age is proposed, with a higher recommended dose in patients under 8 years of age. Based on the adult experience, a comparable lead-in period of 2 weeks is also proposed in paediatric patients. Data on the safety and tolerability data in children have been obtained mostly from

children treated with 120 mg/m^2, but additional data with the proposed dosage will be submitted. The safety profile of nevirapine in children is almost the same compared to adults although granulocytopaenia was more commonly reported in children. Results from completed and ongoing studies will be submitted once available to confirm the clinical benefit of nevirapine in children, including in combination therapy

Overall the bioequivalence between the oral suspension administered with the syringe and the marketed 200 mg tablets has been demonstrated and therefore an approval of the suspension for the adult could be recommended. The use of oral suspension in adults is of particular interest for adults who have difficulties to swallow tablets.

Benefit/risk assessment

The CPMP considered that, on the basis of the current efficacy and safety data, the overall risk/benefit profile for Viramune appears favourable when used in combination therapy. The CPMP therefore recommended on 22 October 1997 the granting for a marketing authorisation under exceptional circumstances for Viramune 200 mg tablets. This opinion was based on the beneficial effect of 400 mg of Viramune administered daily in combination therapy in adult patients with HIV disease, as measured by changes in biological markers and by clinical endpoints. The applicant agreed to provide, as requested by the CPMP, a clinical programme for an expanded investigation of Viramune in combination therapy.

Based on the clinical data obtained in children, the Committee recommended on 25 March 1999 the granting for a marketing authorisation for Viramune 50 mg/5 ml oral suspension for use in antiviral combination treatment in HIV-infected adults and children over 2 months of age patients.

Based on the additional data provided as part of the specific obligations to be fulfilled, the CPMP considered that the benefit/risk profile of Viramune remained favourable. During its deliberation on 25 April 2002, the CPMP advised a conversion of the authorisations under exceptional circumstances into full Marketing Authorisations, for both tablets and oral suspension.

The approved indication for Viramune 200 mg tablets and 50 mg/5 ml oral suspension is:
“Nevirapine is indicated as part of combination therapy for the antiviral treatment of HIV-1 infected patients with advanced or progressive immunodeficiency”.